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October 12, 2000

BOX PATENT APPLICATION  
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Derrick T. Gordon

Name of Person Mailing Paper or Fee

*Derrick T. Gordon*

Signature

October 12, 2000

Date of Signature

Re: New U.S. Patent Application  
ANALYZING APPARATUS  
By: Yoshiaki HATA  
Attorney Docket: 15162/02600

Dear Sir:

Enclosed for filing are the following papers relating to  
ANALYZING APPARATUS, Yoshiaki HATA, inventor:

- (1) Specification (45 pages, including 29 claims and an abstract);
- (2) Executed Declaration and Power of Attorney (5 pages);
- (3) Formal Drawings (10 sheets);
- (4) Transmittal letter (1 page) with PrintEFS Patent Application Bibliographic Data (1 page);

9921 U.S. PTO  
09/689010  
10/12/00

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October 12, 2000

Page 2

- (5) Transmittal letter (1 page) with Certified Copy of Priority Document (53 pages); and
- (6) Assignment (2 pages) of the invention to MINOLTA CO., LTD., with attached Recordation Form Cover Sheet (1 page) (in duplicate).

The amount of the filing fee is calculated below:

			Fee for small entity			Fee for other than small entity	
Fee	No. filed	No. extra *	Rate	Fee	OR	Rate	Fee
Basic fee				\$355	OR		\$710
Total claims	29-20=	9	X \$9=	\$0	OR	X \$18=	\$162
Independent claims	8-3=	5	X \$40=	\$0	OR	X \$80=	\$400
Multiple Dependent Claim Presented	0	0	+\$135=	\$0	OR	+\$270=	\$-0-
			Total	\$0	OR	Total	\$1,272

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Please charge the required fees (\$1,272.00 for the application filing fee and \$40.00 for recordal of the Assignment) to Sidley & Austin's Deposit Account No. 18-1260. If additional fees are due, please charge any fees during the pendency of this application (other than the issue fee) to Deposit Account No. 18-1260. Please credit any overpayment to Deposit Account No. 18-1260.

This transmittal letter is being filed in duplicate.

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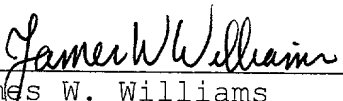
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Assistant Director For Patents  
October 12, 2000  
Page 3

All correspondence is to be directed to the address  
associated with the customer number 24367.

Respectfully submitted,

By:

  
James W. Williams  
Registration No. 20,047  
Attorney for Applicant

JWW/mhg  
Enclosures

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10-13-00

10/12/00  
10689/60  
JC921 U.S. PTO

Attorney Docket No. 15162/02600

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re

U.S. application of: Yoshiaki HATA  
For: ANALYZING APPARATUS  
U.S. Serial No.: To Be Assigned  
Filed: Concurrently  
Group Art Unit: To Be Assigned  
Examiner: To Be Assigned

BOX PATENT APPLICATION

Assistant Director

for Patents

Washington, D.C. 20231

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*Derrick T. Gordon*  
Signature

October 12, 2000

Date of Signature

TRANSMITTAL OF PrintEFS PATENT APPLICATION

BIBLIOGRAPHIC DATA

Submitted herewith is bibliographic data (1 page) for the above-identified application, in the PrintEFS Version 1.0.1 program format.

Respectfully submitted,

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October 12, 2000

Parameter	Value	Unit
Initial concentration	1.0	g/L
Initial pH	7.0	
Temperature	25	°C
Time	0-24	h
Agitation speed	150	rpm
Batch size	100	L
Reactor volume	100	L
Reactor type	Stirred tank	
Impeller type	6-blade	
Impeller diameter	0.15	m
Reactor height	0.5	m
Reactor width	0.15	m
Reactor material	Stainless steel	
Reactor manufacturer	Warriner	
Reactor model	Warriner 100	
Reactor serial number	100	
Reactor location	Warriner	
Reactor date of purchase	10/10/10	
Reactor date of last maintenance	10/10/10	
Reactor date of next maintenance	10/10/10	
Reactor date of decommissioning	10/10/10	
Reactor date of disposal	10/10/10	
Reactor date of recycling	10/10/10	
Reactor date of reuse	10/10/10	
Reactor date of sale	10/10/10	
Reactor date of transfer	10/10/10	
Reactor date of loan	10/10/10	
Reactor date of rental	10/10/10	
Reactor date of lease	10/10/10	
Reactor date of purchase	10/10/10	
Reactor date of last maintenance	10/10/10	
Reactor date of next maintenance	10/10/10	
Reactor date of decommissioning	10/10/10	
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Reactor date of next maintenance	10/10/10	
Reactor date of decommissioning	10/10/10	
Reactor date of disposal	10/10/10	
Reactor date of recycling	10/10/10	
Reactor date of reuse	10/10/10	
Reactor date of sale	10/10/10	
Reactor date of transfer	10/10/10	
Reactor date of loan	10/10/10	
Reactor date of rental	10/10/10	
Reactor date of lease	10/10/10	
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Reactor date of last maintenance	10/10/10	
Reactor date of next maintenance	10/10/10	
Reactor date of decommissioning	10/10/10	
Reactor date of disposal	10/10/10	
Reactor date of recycling	10/10/10	
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Reactor date of sale	10/10/10	
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Reactor date of loan	10/10/10	
Reactor date of rental	10/10/10	
Reactor date of lease	10/10/10	
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Reactor date of last maintenance	10/10/10	
Reactor date of next maintenance	10/10/10	
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Reactor date of disposal	10/10/10	
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Reactor date of sale	10/10/10	
Reactor date of transfer	10/10/10	
Reactor date of loan	10/10/10	
Reactor date of rental		

CORRESPONDENCE INFORMATION

APPLICATION INFORMATION

REPRESENTATIVE INFORMATION

PRIOR FOREIGN APPLICATIONS

Source:: PrintEFS Version 1.0.1

## TITLE OF THE INVENTION

## ANALYZING APPARATUS

This application is based on application No. 11-289319 filed in Japan, the  
5 contents of which are hereby incorporated by reference.

## BACKGROUND OF THE INVENTION

## Field of the Invention

The present invention relates to a technique for analyzing a biotic or  
10 biochemical minute sample, such as analysis of DNA (deoxyribonucleic acid) with  
the use of a technique such as MEMS (Micro Electro Mechanical Systems) or  
MOEMS (Micro Opto Electro Mechanical Systems).

## Description of the Background Art

15 Hitherto, research is made on an apparatus (an apparatus called  $\mu$ TAS or the  
like) that measures a fluorescence of a sample (a minute substance such as DNA) in a  
solution flowing through a minute channel to perform various kinds of analysis. In  
this apparatus, the measurement of fluorescence is realized by individually  
assembling a light source and an optical system for projecting an excited light to a  
20 minute channel and an optical system and an optical detecting element for measuring  
the fluorescence around the apparatus in which the minute channel has been formed.  
For this reason, the assembled system as a whole performs a function of an analyzing  
apparatus.

An example of such an apparatus is disclosed in US Patent No. 5,858,195.

25 This apparatus is constructed in such a manner that a complex biotic or biochemical

operation (analysis or synthesis) to a sample is performed on an analyzing chip (microchip) having a size of about 5 cm × 2.5 cm by an electronic control. Specifically, a plurality of water tanks for storing chemical substances and minute channels connecting the plurality of water tanks are formed on an analyzing chip, and  
5 each water tank has an individually controlled electric potential, which allows a sample to move through the minute channel among the water tanks.

As a detector that measures a sample, the characteristics and others of the sample can be detected by using, for example, those that detect optical absorption, change in refractive index, fluorescence emission, chemical emission, various Raman  
10 spectra, electrical conductivity, electrochemical current, sound wave propagation, or the like.

In performing analysis with the use of an analyzing chip, DNA is divided into fragments having different lengths with a restriction enzyme, and each fragment is allowed to move through a minute channel by electrophoresis. At a certain point  
15 in the minute channel, a light such as laser light for exciting a fluorescence is given from the outside and, when a fragment passes through that point, a prescribed fluorescent dye is excited, and the fragment is analyzed by detecting the fluorescence characteristics with a light-receiving optical system disposed on the outside.

However, the prior art technique such as mentioned above involves a  
20 problem that the size and the cost of the system as a whole increases because the devices such as the optical system that projects laser light or the like for exciting a fluorescence from the outside of the analyzing chip and the optical system for measuring the fluorescence are disposed around the analyzing chip to allow the system to function as an analyzing system. Further, a lot of labor is required for  
25 preparation and position adjustment in disposing each member around the analyzing

chip in which the minute channel has been formed, thereby raising a problem that an efficient analysis cannot be carried out.

Moreover, even if an attempt is made to improve the sensitivity or the SN ratio of the fluorescence measurement by adjusting the optical system and others, it reaches a limit at a comparatively low level, and it is difficult to make a further improvement.

Furthermore, in order to repeat a stable analysis with good efficiency, it is desired to perform supply and pick-up of samples, exchange of analyzing chips, and others automatically. Also, in picking up the samples, it is desired to pick up the object samples easily without performing complex manipulations.

#### SUMMARY OF THE INVENTION

According to a first aspect of the present invention, a microchip includes: a channel having at least one internal surface, wherein an object to be analyzed is capable of traveling through the channel; and an optical element facing the channel to receive a light from the object, the optical element having a surface forming a part of the at least one internal surface of the channel.

Therefore, an optical system and others need not be disposed separately in an analyzing apparatus, so that the analyzing apparatus can be realized in a small scale and at a low cost.

Further, according to a second aspect of the present invention, a microchip includes: a channel extending in an extending direction, wherein an object to be analyzed is capable of traveling through the channel; and deflecting electrodes for deflecting the object in a direction traverse to the extending direction at a vicinity of an analyzing position by being applied with electrical signals thereto.



Therefore, the sample can be transported with certainty along the channel.

Also, the present invention is directed to a manipulating needle for manipulating an object.

According to a third aspect of the present invention, a manipulating needle  
5 includes: an edge portion having a diameter not larger than 50  $\mu\text{m}$ , wherein a material having a capability of a biochemical bond with the object or a capability of a biotic bond with the object is adhered to the edge portion.

Therefore, a specific sample can be picked up alone with ease by a simple operation.

10 Also, the present invention is directed to a manipulator for manipulating an object under a control from an external manipulating apparatus.

According to a fourth aspect of the present invention, a manipulator includes: an edge portion to which a material having a capability of a biochemical bond with the object or a capability of a biotic bond with the object is adhered; and an  
15 attachment portion for being detachably attached with the external manipulating apparatus.

Also, the present invention is directed to an analyzing apparatus.

According to a fifth aspect of the present invention, an analyzing apparatus includes: a holder for detachably holding an analyzing microchip, the analyzing  
20 microchip including a channel having at least one internal surface, wherein an object to be analyzed is capable of traveling through the channel; and a sensor unit, provided in the holder, for receiving a light from an analyzing position of the channel thereby a light from the object is detected by the sensor when the object travels the analyzing position.

25 Therefore, the analyzing apparatus can be realized in a small scale and at a

low cost.

According to a sixth aspect of the present invention, an analyzing apparatus includes: a holder for detachably holding a microchip, the microchip including: a channel extending in an extending direction, wherein an object to be analyzed is capable of traveling through the channel; and deflecting electrodes at least one of which is provided at a vicinity of an analyzing position; and a controller, provided in the holder, for applying electrical signals to the deflecting electrodes, wherein the deflecting electrodes deflects the object in a direction traverse to the extending direction at the analyzing position when the controller applies the electrical signals to the deflection electrodes.

According to a seventh aspect of the present invention, an analyzing apparatus includes: a holder for detachably holding an analyzing microchip, the analyzing microchip including a channel having at least one internal surface, wherein an object to be analyzed is capable of traveling through the channel; and a lifting unit, provided in the holder, for lifting the analyzing microchip.

Also, the present invention is directed to a method of picking up an object traveling in a traveling direction through a channel formed in an analyzing microchip.

According to an eighth aspect of the present invention, the method includes: sensing the object at an analyzing position of the channel; moving, in response to the sensing of the object, a manipulator into a pick up position of the channel that is downstream side of the analyzing position with respect to the traveling direction, wherein at least a part of the manipulator is made of a material having a characteristic of a biochemical bond capability with the object or a biotic bond capability with the object; and retrieving the object by the manipulator by using the characteristic of the material.

Thus, the present invention has been made in view of the prior art technique, and an object thereof is to provide an analyzing apparatus that can be realized in a small scale and at a low cost, and also to provide a microchip, a sample manipulating needle, and a sample picking up method that can pick up a sample with ease.

5           These and other objects, features, aspects and advantages of the present invention will become more apparent from the following detailed description of the present invention when taken in conjunction with the accompanying drawings.

#### BRIEF DESCRIPTION OF THE DRAWINGS

10           Fig. 1 is a perspective view illustrating a construction example of an analyzing apparatus according to the present invention;

            Fig. 2 is a cross section view obtained by cutting a sensor unit with a prescribed plane;

            Fig. 3 is an enlarged view around the sensor section of Fig. 2;

15           Fig. 4 is an enlarged view around a condensing optical element 26 in the A-A cross section of Fig. 2;

            Fig. 5 is a schematic construction view of a micromanipulator;

            Figs. 6A and 6B are views each illustrating an example of a voltage waveform that is applied to a piezoelectric element of a linear actuator;

20           Fig. 7 is a view illustrating an output example of the sensor section;

            Fig. 8 is a view illustrating a method of picking up a sample in a minute channel;

            Fig. 9 is an explanatory view of a mechanism for exchanging sample manipulating needles of a micromanipulator;

25           Fig. 10 is a perspective view illustrating an analyzing apparatus to which a

pot exchanging mechanism is added; and

Fig. 11 is a view illustrating a construction example of analyzing apparatus in which an analyzing chip exchanging mechanism is disposed.

## 5 DESCRIPTION OF THE PREFERRED EMBODIMENTS

Hereafter, preferred embodiments of the present invention will be described with reference to the attached drawings.

### <1. basic construction of an analyzing apparatus>

Fig. 1 is a perspective view illustrating a construction example of an  
10 analyzing apparatus 1 according to this embodiment. The analyzing apparatus 1 is constructed to include a sensor unit 10, an analyzing chip 20, and micromanipulators 30a, 30b.

A hollowed portion for inserting the flat plate like analyzing chip 20 is formed on the upper surface side of the sensor unit 10 and, at the time of sample  
15 analysis, the analyzing chip 20 is inserted into the hollowed portion, whereby the sensor unit 10 and the analyzing chip 20 are integrated together, as shown in Fig. 1.

A plurality of supplying tanks for respectively supplying different samples, a reaction tank for allowing different samples to react in the analyzing chip 20, and a plurality of discharging tanks for discharging the samples having reacted in the  
20 reaction tank are formed on the analyzing chip 20. Specifically, referring to Fig. 1, a sample tank 21a for supplying a sample solution containing a sample as an object of analysis, and a reagent tank 21b for supplying a reagent to be used for analysis are formed as the plurality of supplying tanks, and minute channels 24a, 24b are formed from these tanks to the reaction tank 22. Further, an extracting tank 23a for  
25 eventually guiding the reaction product as an object of extraction, an exhaust tank

23b for eventually storing unnecessary solutions, and a buffer tank 23c for storing a buffer solution for allowing the reaction product to move towards the extracting tank 23a are formed as the plurality of discharging tanks. The reaction tank 22 and the exhaust tank 23b are connected with each other by minute linear channels 24c, 24e; the extracting tank 23a and the buffer tank 23c are connected with each other by minute linear channels 24d, 24f; and the minute channels 24d, 24f intersect perpendicularly with the minute channel 24c from the reaction tank 22 at an intersection point P.

Each of these tanks is a recess provided on the surface of the analyzing chip 20, and is formed to have the same depth as the minute channels 24a to 24f that are carved in the surface of the analyzing chip. Further, the minute channels 24a to 24f are covered with a cover plate 25, and is formed as a pipe passageway. Here, the minute channels 24a to 24f are each formed to have a width of about 60  $\mu\text{m}$  and a depth of about 10 to 20  $\mu\text{m}$ .

Samples such as a sample solution and a reagent are either directly supplied to each supplying tank on the analyzing chip 20 or put into supplying pots (vessels) 41 that can be easily handled with, such as a sample pot 41a or a reagent pot 41b, and supplied to the sample tank 21a or the reagent tank 21b on the analyzing chip 20 from each pot. Supply of the samples from each pot 41 to each tank is carried out by a first micromanipulator 30a provided for supplying samples. The samples supplied to each supplying tank moves through the minute channel towards the reaction tank and the discharging tank by electrophoresis. The sample as an object of extraction, which has been eventually guided to the extracting tank 23a, is stored into the extracting pot 51 by a second micromanipulator 30b.

Fig. 2 is a cross section view obtained by cutting the sensor unit 10 with an

XZ-plane including the minute channel 24c.

Referring to Fig. 2, a hollowed portion for inserting the flat plate-like analyzing chip 20 is formed on the upper surface side of the sensor unit 10 and, on the inner side thereof, a sensor section 11, a controller section 12, and electrodes 13a, 13b are provided. The sensor section 11 is disposed in an opening 10a provided in the hollowed portion, and is constructed to be capable of taking the light on the upper side of the opening 10a into the inside. Further, the upper surface sides of the electrodes 13a, 13b are formed as connectors 14a, 14b each having a prescribed area. The controller section 12 receives the light detected by the sensor section 11 as electric signals and applies a voltage to each of the electrodes 13a, 13b.

Here, in Fig. 2, only two electrodes 13a, 13b are illustrated; however, electrodes controlled by the controller section 12 are provided for each tank formed in the analyzing chip 20.

On the other hand, when the analyzing chip 20 is inserted into the hollowed portion of the sensor unit 10, the connectors 28a, 28b joined with the connectors 14a, 14b are formed on the lower surface side of the analyzing chip 20, and electrophoresis electrodes 29a, 29b that passes through the inside of the analyzing chip 20 to reach near the upper surface of each tank are connected from the connectors 28a, 28b, respectively. In other words, the electrophoresis electrodes 29a, 29b are buried in the analyzing chip 20, and one end thereof protrudes into each tank on the analyzing chip 20, and the other end thereof is provided with the connectors 28a, 28b for giving an electric potential from the sensor unit 10. Further, a tapered hole 20a is formed at a prescribed position on the lower side of the minute channel 24c formed in the analyzing chip 20, and a condensing optical element 26 is disposed in the hole 20a. The position where the condensing optical element 26 is disposed is designed and

fabricated so as to be at a position above the sensor section 11 in the sensor unit 10 when the analyzing chip 20 is mounted onto the sensor unit 10.

Therefore, when the analyzing chip 20 is mounted to the sensor unit 10, the connectors 14a, 14b are joined with the connectors 28a, 28b, respectively, and the  
5   condensing optical element 26 and the sensor section 11 are integrated to perform an optical function, thereby making it possible to perform measurement of fluorescence in the minute channel 24c well. Further, in the mounted state such as in Fig. 2, by means of the controller section 12 setting the electrophoresis electrode 29a at a low  
10   electric potential and setting the electrophoresis electrode 29b at a high electric potential, an electric field in the X-direction is generated in the minute channel 24c, whereby the sample moves by electrophoresis from the sample tank 21a towards the exhaust tank 23b.

Details of the principle of the optical function realized by integration of the condensing optical element 26 and the sensor section 11 are described in “Highly  
15   efficient detection of surface-generated fluorescence” given in a known document: Applied Optics /Vol. 38, No. 4/1 February 1999 (pp. 724-732). This document describes a method of measuring fluorescence by capturing a fine and weak light with a condensing optical element having a shape obtained by cutting a tip end of a paraboloid of revolution made of glass with a plane being perpendicular to the  
20   rotation axis and containing a point near the focal point, and allowing a condensing lens to converge the parallel light, which has been reflected by the paraboloid of the condensing optical element, into an optical detecting element such as an avalanche photodiode.

In this embodiment also, the fluorescence of the sample is measured by a  
25   similar technique. Fig. 3 is an enlarged view around the sensor section 11 of Fig. 2.

Referring to Fig. 3, a condensing optical element 26 for capturing fluorescence from a fluorescent marker adhered to minute particles (samples) such as DNA that migrate through the minute channel 24c is mounted at a prescribed position of the minute channel 24c of the analyzing chip 20. Further, a condensing lens 11a, a mask plate 11b, and an optical detecting element 11c are provided in the sensor section 11 of the sensor unit 10, and are constructed in such a manner as to be capable of measuring fluorescence from the fluorescent marker adhered to the sample in the minute channel 24c by converging the parallel light obtained from the condensing optical element 26 to the optical detecting element 11c by means of the condensing lens 11a.

The condensing optical element 26 is disposed so that the light-taking surface 26a, which is a plane formed by the above-mentioned cutting, faces the minute channel 24c, so that the fluorescence can be efficiently captured if the fluorescent marker comes near to the light-taking surface. Particularly, if the fluorescent marker can be approximated within about 100 nm from the light-taking surface 26a, the light which is usually reflected by the light-taking surface 26a constituting an interface between the solution and the condensing optical element 26 is taken as an evanescent light into the condensing optical element 26 by a so-called near field effect, thereby making it possible to improve an overall sensitivity in the fluorescence measurement. In other words, by approximating a fluorescence-generating sample to a plane containing a point near the focal point, the fluorescence can be captured efficiently into the condensing optical element 26 and, by allowing the light reflected by the paraboloid to be incident into the optical detecting element 11c such as an avalanche photodiode by the condensing lens 11a, a highly sensitive sensing can be carried out. The light taken into the condensing optical element 26 is



reflected by the paraboloid of the condensing optical element 26 and is emitted from the condensing optical element 26 as an approximately parallel light.

A mask plate 11b having a pinhole is disposed immediately before the optical detecting element 11c, and an image of the pinhole is formed near the light-taking surface 26a of the condensing optical element 26 in the analyzing chip 20 so as to cut off a background light from a portion located away from the light-taking surface 26a. If a fine and weak light is to be measured, it is essential to separate the background light from the light to be measured. Therefore, by means of the mask plate 11b, unnecessary scattered light and excited light can be effectively cut off and, as a result, the SN ratio of the measured value in the sensor section 11 is improved.

The relative position of the condensing optical element 26 on the analyzing chip 20 to the condensing lens 11a on the sensor unit 10 side must be precisely set. Therefore, in order that the analyzing chip 20 is mounted to the sensor unit 10 with good precision, it is desirable to control the precision of the outer shape of the analyzing chip 20 and the electrical and optical connecting part thereof to the sensor unit 10 and the precision of the hollowed portion (carved portion) of the sensor unit 10 where the analyzing chip 20 is to be inserted and the electrical and optical connecting part thereof to the analyzing chip 20, strictly within prescribed precision ranges.

Further, in order to raise the condensing efficiency as described above, the fluorescence-generating sample must be approximated within about 100 nm from the light-taking surface 26a of the condensing optical element 26, so that deflecting electrodes 44, 45 are provided near the condensing optical element 26 and in the inside of the minute channel 24c. Namely, the deflecting electrodes 44, 45 perform a function of approximating the sample in the minute channel 24c to the condensing

optical element 26.

Further, by applying an electric field between the deflecting electrodes 44, 45, the sample such as DNA can be deflected in a direction traverse to the minute channel 24c. Specifically, the deflecting electrode 44 is disposed at a position facing the minute channel 24c of the cover plate 25, and the deflecting electrode 45 is disposed at an upstream side of the position where the condensing optical element 26 is disposed in the minute channel 24c and on the bottom surface of the minute channel 24c. The electric potential given to these deflecting electrodes 44, 45 are constructed to be controlled from the controller section 12 on the sensor unit 10 side by a joining mechanism with the sensor unit 10 in the same manner as the previously mentioned electrodes for electrophoresis. By setting the deflecting electrode 44 at a lower voltage than the deflecting electrode 45, the controller section 12 can allow the fluorescence-generating sample to migrate to a vicinity of the bottom surface in the minute channel 24c. As a result, the sample can be approximated to the neighborhood of the light-taking surface 26a of the condensing optical element 26. In order to prevent generation of air bubbles by electrolysis of the solution at the deflecting electrode part, particles may be approximated to the condensing optical element by dielectric phoresis due to an electric field gradient generated by applying an alternating current electric field between the deflecting electrodes. Also, the sample can be attracted to the deflecting electrode 45 by the action of the electrophoresis or dielectric phoresis, whereby the intensity and the spectrum of the fluorescence can be measured with precision in a state in which the movement along the minute channel 24c is stopped.

Fig. 4 is an A-A cross section view of the analyzing apparatus 1 in Fig. 2, showing an enlarged view around the condensing optical element 26. Referring to

Fig. 4, the minute channel 24c has a trapezoidal cross section in which the upper bottom thereof is longer than the lower bottom thereof, and each side surface is a sloped surface. The electric potential applied to the above-mentioned deflecting electrodes 44, 45 from the controller section 12 is supplied into the minute channel 24c via the connectors 28c, 28d.

Further, referring to Fig. 4, a light source 15 for exciting the fluorescence is provided in the sensor unit 10. The light source 15 for use may be any light source such as a laser, a LED, or a lamp of various type, in accordance with the fluorescent marker to be used. The light source 15 emits a prescribed excited light towards the upper side. In order to guide the excited light from the light source 15 into the minute channel 24c, a light guide 27 is provided as a light guiding means in the inside of the analyzing chip 20. The light guide 27 can be constructed by using an optical fiber buried in the analyzing chip 20 or by providing a wave guide in the analyzing chip 20.

The tip end of the light guide 27 faces the minute channel 24c and, at a position where the light guide 27 is disposed, the light-emitting surface of the light guide 27 is a side wall surface of the minute channel 24c. Further, the light-emitting surface of the light guide 27 is also formed to have a slope similar to that of the side surface of the minute channel 24c. As a result, the light emitted from the light-emitting surface of the light guide 27 generates a refractive action at the light-emitting surface, whereby the excited light is radiated towards the bottom surface side of the minute channel 24c. In other words, it is constructed in such a manner that the excited light is radiated in concentration to the light-taking surface 26a of the condensing optical element 26.

Here, Fig. 4 shows that the light emitted from the light guide 27 is refracted

at the side surface of the minute channel 24c to be directed towards the center of the light-taking surface 26a of the condensing optical element 26; however, a microlens or a diffractive optical element may be attached to the end portion of the light guide 27 to control the direction of the excited light and the width of the light beams.

5 Further, when the fluorescence is measured by the sensor section 11 and it is found out that minute particles (samples) such as DNA, which is an object of extraction, have passed through the channel above the sensor section 11, channels may be switched according to the principle of electrophoresis to guide the sample as an object of extraction to the extracting tank 23a, or the sample may be picked up by  
10 means of a micromanipulator 30b to realize a function as an extracting means, whereby the sample as an object of extraction is taken out and utilized for various purposes.

In the case of extraction by switching the channels, the controller section 12 may set the electric potential of the buffer tank 23c shown in Fig. 1 to be lower than  
15 the electric potential of the extracting tank 23a and may set the electric potential of the exhaust tank 23b to be a suitable electric potential lower than that of the extracting tank 23a, whereby the sample as an object of extraction is allowed to proceed in the left direction from the intersection point P to be guided to the extracting tank 23a.

20 Further, by the action of the micromanipulator 30b taking out the solution in the extracting tank 23a and storing the solution into the extracting pot 51, the sample as an object of extraction can be collected in the extracting pot 51.

Thus, by incorporating a super small-scale and highly sensitive fluorescence detecting mechanism into the analyzing apparatus 1, biotic or biochemical analysis  
25 such as an analysis of DNA can be performed at a high speed in a small and

inexpensive apparatus. In other words, in this embodiment, the mechanism for fluorescence detection is incorporated in the analyzing apparatus 1 which is constructed with the sensor unit 10 and the analyzing chip 20, so that there is no need to dispose an optical system separately around the apparatus. Therefore, the analysis  
 5 process can be started speedily, and scale reduction and cost reduction can be achieved.

Also, since a highly sensitive fluorescence detecting mechanism is realized, a good analysis can be made even with one molecule or several molecules, thereby reducing the amount of required samples such as a sample as an object of analysis and  
 10 a reagent to the minimum. For this reason, the analysis from a minute sample can be made and, in the field of analysis of DNA, an amplification work such as polymerase chain reaction (PCR) that is performed in advance can be omitted or the number of repetitions thereof can be reduced.

Also, by providing the micromanipulators 30a, 30b in the analyzing  
 15 apparatus 1, manipulation of the minute samples (supply or extraction manipulation) can be performed automatically.

Further, in the analyzing apparatus 1, the optical system for detecting fluorescence is set in an optimal state simply by inserting the analyzing chip 20 into the sensor unit 10, so that an adjustment or the like of the optical system does not  
 20 need time and the preparation time for the sample analysis can be shortened.

## <2. micromanipulator>

Here, the construction of the micromanipulators 30a, 30b will be described.

Fig. 5 is a schematic construction view of the micromanipulator 30a.

The micromanipulator 30a is constructed to include a first linear actuator 31,  
 25 a second linear actuator 32, a third linear actuator 33, and rotary actuator 34. An

end effector 35 is attached to the tip end of the rotary actuator 34 in a freely attachable and detachable manner.

The first to third linear actuators 31 to 33 are sequentially linked so as to perpendicularly intersect with each other, and a plurality of degrees of linear  
5 movement freedom is realized. Further, the rotary actuator 34 is constructed to be capable of changing the posture of the end effector 35 coupled to the tip end of the rotary actuator 34 to an arbitrary angle.

The first linear actuator 31 includes a piezoelectric element 31a, a spline shaft 31b, and a slider 31c, and is constructed to be capable of moving the slider 31c  
10 along the Z-axis direction.

The piezoelectric element 31a is constructed with laminated piezoelectric ceramics or the like and is connected to the controller section 12. The piezoelectric element 31a performs an elongation and contraction operation along the Z-axis direction by application of a voltage from the controller section 12. One end side of  
15 the piezoelectric element 31a is affixed to the fringe side of the sensor unit 10 and the other end side is affixed to the end surface of the spline shaft 31b. Therefore, by the elongation and contraction operation of the piezoelectric element 31a, the spline shaft 31b moves in the Z-axis direction which is the longitudinal direction of the spline shaft 31b.

20 Further, the slider 31c is fitted into the spline shaft 31b and, since an elastic member mounted in the inside of the slider 31c generates a certain friction between the slider 31c and the spline shaft 31b, the slider 31c is usually in a state of being fixed to the spline shaft 31b. Here, needless to say, the rotation of the slider 31c in the circumferential direction of the spline shaft 31b can be restrained by an  
25 engagement of the projection of the spline shaft 31b and the recess of the slider 31c.

The second linear actuator 32 is fixed to the slider 31c of the first linear actuator 31 and, in the same manner as the first linear actuator 31, the second linear actuator 32 is constructed to include a piezoelectric element 32a connected to the controller section 12, a spline shaft 32b, and a slider 32c, and is adapted to be capable of moving the slider 32c along the X-axis direction. Further, the third linear actuator 33 is fixed to the slider 32c of the second linear actuator 32 and, in the same manner as each of the above-mentioned linear actuators, the third linear actuator 33 is constructed to include a piezoelectric element 33a connected to the controller section 12, a spline shaft 33b, and a slider 33c, and to be capable of moving the slider 33c along the Y-axis direction.

Further, the rotary actuator 34 is affixed to the slider 33c of the third linear actuator 33 along the Z-axis direction. The rotary actuator 34 includes a stepping motor 34a, a rotating plate 34b, and a pitch-yaw actuator 34c.

The stepping motor 34a is constructed with a tubular main body having a small diameter, and is fixed to the slider 33c of the third linear actuator 33. The stepping motor 34a is connected to the controller section 12 and is constructed in such a manner that, by energization from the controller section 12 to the stepping motor 34a, the rotating plate 34b linked to a rotor disposed in the inside of the stepping motor 34a rotates around the rotation axis of the stepping motor 34a. Here, in Fig. 5, the rotation axis of the stepping motor 34a is disposed to be parallel to the Z-axis. The stepping motor 34a allows a rotation movement around a rotation axis parallel to the Z-axis among the rotary operations.

One end side of the pitch-yaw actuator 34c is attached to the rotating plate 34b, and the pitch-yaw actuator 34c rotates around the rotation axis of the stepping motor 34a in accordance with the rotation of the rotating plate 34b. Further, a

prescribed oblique plate is disposed at the other end of the pitch-yaw actuator 34c and has a construction of a pivot bearing. By energization from the controller section 12 to a wire made of a shape-memorizing alloy stretched in the inside, the wire elongates or contracts, whereby the oblique plate can be tilted in any direction.

5 Thus, it is constructed in such a manner that, by driving the pitch-yaw actuator 34c, the oblique plate is tilted from a state of being parallel to the XY-plane to any direction and angle. The pitch-yaw actuator 34c makes it possible to perform a rotation operation (pitching) around a rotation axis parallel to the X-axis and a rotation operation (yawing) around a rotation axis parallel to the Y-axis among the  
10 rotary operations.

A base side of the end effector 35 of the micromanipulator 30a is connected and disposed at a tip end of the rotary actuator 34. As the end effector 35, those having a mechanism suitable for performing a prescribed manipulation to minute samples such as DNA are adopted. For example, a micropipette capable of storing  
15 and ejecting a prescribed amount of solution, a needle having its tip end formed to have a minute diameter of about 1 to 50  $\mu\text{m}$ , and others are used as the end effector 35.

The micromanipulator 30a is constructed as described above; the first to third linear actuators 31 to 33 can move the position of the end effector 35 linearly in  
20 the three axis directions of X, Y, Z; and the rotary actuator 34 can rotate the end effector 35 in the three directions of rolling, pitching, and yawing. In other words, the above-mentioned construction realizes a sum of six degrees of freedom, i.e. three degrees of freedom for linearly moving the end effector 35 and three degrees of freedom for rotating the end effector 35. Here, the three degrees of freedom for  
25 rotation are realized by a roll angle movement performed by the stepping motor 34a



and a pitch angle and yaw angle movement performed by the pitch-yaw actuator 34c.

Therefore, by adopting the construction of the micromanipulator 30a such as described above, the end effector 35 can be moved to any position and also the end effector 35 can be changed to any posture.

5 Here, the linear movement performed by the first linear actuator 31 will be described. Figs. 6A and 6B are views illustrating a non-symmetric voltage waveform such as a saw-tooth waveform as an example of the voltage waveform applied to the piezoelectric element 31a. Fig. 6A illustrates a voltage waveform in the case of moving the slider 31c in the +Z direction and Fig. 6B illustrates a voltage waveform in the case of moving the slider 31c in the -Z direction.

10 In this embodiment, when a negative voltage is applied to the piezoelectric element 31a, the piezoelectric element 31a contracts; conversely, when a positive voltage is applied to the piezoelectric element 31a, the piezoelectric element 31a elongates. The amount of elongation or contraction can be varied by the absolute value of the applied voltage. For this reason, the amount of elongation or contraction can be controlled by controlling the voltage applied to the piezoelectric element 31a. As a result, movement along the Z-axis of the spline shaft 31b can be controlled.

20 For example, the voltage waveform of Fig. 6A shows a moderate slope in the rising part of the voltage waveform, and shows a sharp slope in the falling part of the voltage waveform. Therefore, at the rising part where the saw-tooth waveform is moderate, the slider 31c is integrated with the spline shaft 31b by a friction force between the spline shaft 31b and the slider 31c, and moves along the Z-axis direction in accordance with the amount of elongation or contraction of the piezoelectric element 31a. On the other hand, at the falling part where the saw-tooth waveform is

25

sharp, the piezoelectric element 31a tends to suddenly return to the original position while a large inertia force is generated in the slider 31c whereby the slider 31c tends to stay at the position after the movement. This inertia force becomes larger than the friction force, whereby sliding occurs between the slider 31c and the spline shaft 31b. As a result, the slider 31c moves in the +Z direction for the sliding length of the slider 31c relative to the spline shaft 31b. Thus, by repeatedly giving a saw-tooth waveform such as shown in Fig. 6A to the piezoelectric element 31a, the slider 31c moves to the +Z direction side stepwise along the spline shaft 31b.

On the other hand, the voltage waveform of Fig. 6B has a polarity opposite to the waveform of Fig. 6A. Therefore, at the rising part where the saw-tooth waveform is moderate, the slider 31c is integrated with the spline shaft 31b by a friction force between the spline shaft 31b and the slider 31c, and moves along the Z-axis direction in accordance with the amount of elongation or contraction of the piezoelectric element 31a. Since the piezoelectric element 31a contracts by being applied with a negative voltage, the piezoelectric element 31a contracts gradually at the moderate rising part of Fig. 6B. On the other hand, at the sharp falling part of Fig. 6B, the piezoelectric element 31a tends to suddenly return to the original state from the contracted state thereby generating a large inertia force in the slider 31c. This inertia force becomes larger than the friction force, whereby sliding occurs between the slider 31c and the spline shaft 31b. As a result, the slider 31c moves in the -Z direction for the sliding length of the slider 31c relative to the spline shaft 31b. Thus, by repeatedly giving a saw-tooth waveform such as shown in Fig. 6B to the piezoelectric element 31a, the slider 31c moves to the -Z direction side stepwise along the spline shaft 31b.

Thus the first linear actuator 31 is constructed in such a manner that, by

reciprocating the piezoelectric element 31a serving as a driving means at non-symmetric speeds, the first linear actuator 31 can reciprocate the spline shaft 31b connected to the piezoelectric element 31a, whereby the slider 31c is capable of relative inertia movement. Here, if the applied voltage in driving the piezoelectric  
5 element 31a is strictly controlled, the amount of movement for which the slider 31c moves by one slide can be controlled to an almost constant value. In other words, if the voltage level or the slope of the waveform of the applied voltage is controlled, the amount of movement for which the slider 31c moves by one slide can be varied. For example, if the voltage level is set high and the slope of the sharp falling part is made  
10 sharper, the amount of movement caused by one slide increases, whereby the end effector 35 can be moved at a high speed. Conversely, if the voltage level is set low and the slope of the sharp falling part is made a little moderate, the amount of movement caused by one slide decreases, whereby the end effector 35 can be moved little by little at a low speed.

15 Further, if a saw-tooth waveform such as mentioned above is continuously applied to the piezoelectric element 31a, the operation of the slider 31c will be a rough movement of stepwise motion. On the other hand, by controlling the voltage value applied to the piezoelectric element 31a, the piezoelectric element 31a shows an amount of elongation or contraction corresponding to the voltage value, so that the  
20 operation of the slider 31c will be a fine movement of continuous motion in a minute range. Therefore, by using a piezoelectric element as a source of driving the linear actuator, the rough movement and the fine movement can be used separately, whereby the position precision of the slider 31c can be enhanced.

Here, by forming a magnetization pattern forming portion at the projecting  
25 part of the spline shaft 31b and further disposing a magnetic resistance element or the

like in the inside of the slider 31c, they are integrated to construct a linear encoder, and a pulse signal can be generated from the magnetic resistance element in accordance with the amount of movement of the slider 31c. By performing a prescribed operation based on the pulse signal, the position of the slider 31c relative to the spline shaft 31b can be detected, and the movement can be controlled on the basis of this position.

As shown above, the operation of the first linear actuator 31 has been described; however, the second linear actuator 32 and the third linear actuator 33 have the same construction and operation as the first linear actuator 31. Further, in the above, description has been made taking the micromanipulator 30a as an example; however, the micromanipulator 30b is also constructed in the same manner and its operation is the same.

These micromanipulators 30a, 30b are disposed at two end sides of the side of supplying the samples and the side of extracting the samples in the sensor unit 10, as shown in Fig. 1, and are constructed in such a manner that an electric controlling signal is supplied to each actuator by the controller section 12 in the sensor unit 10.

Furthermore, the micromanipulators 30a, 30b such as described above can be housed in a size of about 20 mm cube and can control the end effector 35 with a resolution of around 1  $\mu\text{m}$ , so that the micromanipulators 30a, 30b can be incorporated in the apparatus to perform operations of precision without enlarging the size of the analyzing apparatus 1.

### <3. analyzing operation in the analyzing apparatus>

Returning to Fig. 1, samples such as a sample solution and a reagent supplied by the sample pot 41a and the reagent pot 41b are supplied respectively to the sample tank 21a and the reagent tank 21b in required amounts by the first

micromanipulator 30a mounted to an end of the sensor unit 10. A micropipette capable of putting a prescribed amount of solution in and out is attached to the tip end of the micromanipulator 30a, whereby solutions can be supplied from each pot to each tank.

5           The minute channels 24a to 24f of the analyzing chip 20 are filled with a solution such as a buffer liquid in advance to expel air from the channels so that the supplied sample or reagent can immediately move in the minute channels 24a to 24f by a method such as electrophoresis.

10           The sample and the reagent supplied to the sample tank 21a and the reagent tank 21b move downstream (towards the direction of the exhaust tank 23b) through the minute channels 24a to 24f by electrophoresis. At this time, the sample tank 21a and the reagent tank 21b are set at a lower electric potential than the exhaust tank 23b to generate an electric field that is oriented to an upstream of the minute channels 24a to 24c so that a flow is generated by electrophoresis in a direction opposite to the  
15           electric field. The sample and the reagent meet and react in the reaction tank 22.

          Here, a description will be given on a case in which a solution of plural kinds of DNA fragments cut by a restriction enzyme is used as the sample solution and a solution of plural kinds of probe DNA labeled with a fluorescent marker and having a base sequence that is complementary to the plural kinds of DNA fragments  
20           in the sample solution is used as the reagent.

          When prescribed solutions are supplied to the sample tank 21a and the reagent tank 21b, the sample and the reagent move towards the reaction tank 22 by electrophoresis caused by an electric field applied between the sample tank 21a and the reagent tank 21b and the reaction tank 22. In the reaction tank 22, a portion of  
25           the sample DNA constructed with the DNA fragments and the probe DNA having

complementary base sequences hybridize with each other. The DNA that has hybridized and the DNA that has not hybridized in the reaction tank 22 move downstream (in the direction of the exhaust tank 23b) through the minute channel 24c by electrophoresis caused by the electric field applied between the reaction tank 22 and the exhaust tank 23b. The minute channel 24c between the reaction tank 22 and the intersection point P is filled with a polymer such as polyacrylamide and is constructed to be capable of giving a difference in the phoresis speed in accordance with the size of the DNA that migrates by electrophoresis.

If the lengths of the probe DNAs in the reagent are about the same, the probe DNAs that have not hybridized move at about the same speed through the minute channel 24c by electrophoresis. The DNA fragments (sample DNA) that have not hybridized move through the minute channel 24c at a speed corresponding to their length.

On the other hand, those obtained by hybridization of the probe DNA and the sample DNA have a double chain in the hybridized portion and have a one-chain nucleotide before and after the hybridized portion, constituting a long DNA fragment as a whole. Therefore, those obtained by hybridization move through the minute channel 24c at a slower speed than the probe DNA or the sample DNA that has not hybridized. The type of the DNA fragments in the sample DNA can be analyzed by measuring the difference in the speed of electrophoresis by setting a position of cutting with a restriction enzyme and a base sequence of the probe DNA to be hybridized so that the length of the hybridized DNA will vary depending on the type of the DNA fragments in the sample.

Since a sensing position (position at which the condensing optical element is to be disposed) for measuring the fluorescence of the fluorescent marker

attached to the probe DNA is set at a prescribed position on a little upstream side from the intersection point P of the minute channel 24c, the time at which the probe DNA that has not hybridized passes through the sensor section 11 and the time at which the plural kinds of products obtained by hybridization of the probe DNA and the sample DNA pass through the sensor section 11 can be determined from the output of the optical detecting element 11c in the sensor section 11. Since the DNA fragments (sample DNA) that have not hybridized do not have a fluorescent marker, they do not affect the sensor output.

Fig. 7 is a view showing an output example of the sensor section 11. In this example, the probe DNA that has not hybridized passes through the sensing position at a comparatively early time  $t_1$  after the start of the measurement, and at that time, the first output peak PK1 appears. Thereafter, a plurality of peaks PK2, PK3, PK4 appear at the time  $t_2$ ,  $t_3$ ,  $t_4$ , respectively. In other words, plural kinds of products obtained by hybridization of the probe DNA and the sample DNA pass through the sensing position with a time difference corresponding to the difference in length with time intervals after the probe DNA that has not hybridized passed through the sensing position, whereby the plural peaks PK2 to PK4 appear. The time of appearance of the peak is determined in accordance with the length of each product, and the size of the peak is determined in accordance with the amount of each product. Therefore, the type and other characteristics of the product can be found out by analyzing the output example of Fig. 7. Thus, if there are three types of hybridized products, peaks PK2, PK3, PK4 appear due to the hybridized products as shown in Fig. 7.

Further, by any combination of the selection of a restriction enzyme and the design of the base sequence of the probe DNA, base sequence information such as the

presence of gene modification or one-base polymorphism of the DNA as an object of analysis can be obtained.

Further, if the fluorescent marker for labeling the probe DNA is changed for each type of the probe and the sensor section 11 is constructed to have a spectrum function, the type of the hybridized product can be distinguished by classifying the wavelength of the fluorescence of the marker. In this case, the time at which the hybridized product passes through the sensing position need not be precisely measured, and it is sufficient to distinguish between the peak of the probe DNA that has not hybridized and the peak of the hybridized product in time.

Thus, if it is found that the product as an object of extraction has passed through the sensing position as a result of measurement of the fluorescence in the sensor section 11, control is made to take out an object product by switching the minute channels using the above-mentioned principle of electrophoresis to guide the product as an object of extraction to the extracting tank 23a or by picking up the product with the micromanipulator 30b.

#### <4. taking out the sample>

Here, a method of taking out a sample such as DNA from a minute channel by picking up will be described.

Fig. 8 is a view illustrating a method of picking up DNA in a minute channel. A sample operating needle 35a is used as the end effector that is joined with the tip end of the micromanipulator 30b. The sample operating needle has a base portion 36 and a needle 37 having a small diameter and protruding from the base portion 36. The needle 37 may be made by fine processing of metal or made of whiskers. In order to reduce the turbulence of the flow of solution in the minute channel 24c, at least a tip end portion of the needle 37 that is dipped into the solution



is preferably narrowed to about 1  $\mu\text{m}$  to 50  $\mu\text{m}$ . A capturing DNA 38 is adhered to the tip end of the needle 37. The adhesion of the capturing DNA 38 to the tip end of the needle 37 can be performed by a chemical technique. An example of this technique is disclosed in US Patent No. 5,789,167 as a process for bonding a probe DNA. For example, in this example, a method can be utilized in which an end portion of a polypeptide spacer is bonded to the capturing DNA and the needle 37 by covalent bond.

In Fig. 8, the sensor section 11 detects the movement of the DNA (object DNA) 7 as an object of extraction in the minute channel 24c in a state of being hybridized with the probe DNA 8 having a fluorescent marker 9 attached thereto. At this time, on the basis of the detection result by the sensor section 11, the controller section 12 controls the micromanipulator 30b, and allows the sample operating needle 35a, which is attached as an end effector of the micromanipulator 30b, to be dipped into the solution in the minute channel from a small hole 25a provided in the cover plate 25 on the minute channel 24c. As described above, the tip end (needle 37) of the sample operating needle 35a is formed to have a minute diameter, and a substance having a biotic or biochemical bond capability with the sample to be extracted is adhered to its tip end. The sample to be extracted can be taken out from the solution by dipping the needle 37 in the solution, reacting and bonding the substance adhered to the needle 37 with the sample to be extracted in the solution, and thereafter controlling the operation of the micromanipulator 30b with a control signal from the controller section 12 to take out the needle 37 from the solution.

In this embodiment, the capturing DNA 38 that hybridizes with an object DNA to be extracted is adhered to the needle 37 of the sample operating needle 35a, and the product to be extracted is captured by reacting (hybridizing) the object DNA

contained in the product in the minute channel 24c with the capturing DNA 38.

In other words, by dipping the needle 37 of the sample operating needle 35a into the solution, the capturing DNA 38 adhering to the tip end of the needle 37 hybridizes with the product in the solution, whereby only the object sample can be  
5 extracted from the solution. At this time, if the operation of the micromanipulator 30b is controlled by the controller section 12 so that the tip end of the sample operating needle 35a scans the cross section of the minute channel 24c, the probability of the capturing DNA 38 hybridizing with the object DNA can be increased to ensure a more certain take-out of the object sample.

10 As described above, the DNA picked up from the minute channel 24c is conveyed into the extracting pot 51 by the operation of the micromanipulator 30b, and is stored in the extracting pot 51.

Several processes can be considered when the sample is transported to the extracting pot 51.

15 As an example, there is a process such that a buffer solution is put into the pot in advance, and a hybridized DNA is dipped into the buffer solution together with the sample operating needle 35a. By raising the temperature of the liquid contained in the pot, the bond between the probe DNA and the object DNA is released to make a state in which the object DNA hybridized with the capturing DNA is adhering to the  
20 sample operating needle 35a. Then, the sample operating needle 35a is moved to a different pot filled with a buffer solution and, by raising the temperature of the liquid contained in the pot, the bond between the object DNA and the capturing DNA is released to allow only the object DNA to be present in the solution. In this case, it is necessary to design the base sequences of the probe DNA and the capturing DNA  
25 in accordance with the base sequence of the object DNA so that the bond between the

probe DNA and the object DNA is released at a lower temperature than the bond between the capturing DNA and the object DNA. Then, the temperature raised in the second pot is set higher than the temperature raised in the first pot thereby to release the two bonding sites of the object DNA in a desired order.

5 As another example, the picked-up DNA is heated together with the sample operating needle 35a in the buffer solution of the extracting pot 51 to release the bond between the capturing DNA and the object DNA, thereby to allow the object DNA bonded to the probe DNA to be present in the buffer solution. If the base sequence of the probe DNA is designed to be capable of being used also as a primer for  
10 amplification of the object DNA by polymerase chain reaction (PCR), the object DNA can be amplified simply by adding a polymerase enzyme and oligonucleotide into the extracting pot 51 and controlling the temperature.

Fig. 9 is a view for describing a mechanism of exchanging the sample operating needles 35a of the micromanipulator 30b.

15 Referring to Fig. 9, a plurality of sample operating needles 35a are stored by being inserted into a holder 39. A preserving liquid is put in a prescribed amount into the holder 39 in accordance with the needs to dip the needle point of the sample operating needles 35a. At the time of use, the controller section 12 controls the operation of the micromanipulator 30b to bond the base portion 36 of the sample  
20 operating needle 35a with the tip end of the rotary actuator 34 of the micromanipulator 30b. If the base portion 36 of the sample operating needle 35a is formed of a magnetic material and a magnet or an electromagnet is disposed at the tip end of the rotary actuator 34 of the micromanipulator 30b, the sample operating needle 35a can be easily bonded with the tip end of the rotary actuator 34 of the  
25 micromanipulator 30b. Further, by providing a recess for inserting the base portion

36 of the sample operating needle 35a into the tip end of the rotary actuator 34 in the micromanipulator 30b, the sample operating needle 35a can be mounted so as not to waver during the operation. A precise position control can be made by the micromanipulator 30b if the shapes of the base portion 36 and the needle 37 are  
5 controlled with a prescribed precision in the sample operating needle 35a.

Further, when the controller section 12 allows the micromanipulator 30b to access an arbitrary sample operating needle among the plurality of sample operating needles 35a inserted into the holder 39 and moves the tip end of the rotary actuator 34 to an upper side of the base portion 36, the sample operating needle can be mounted  
10 to the micromanipulator 30b.

On the other hand, in exchanging the sample operating needles, the operation control performed by the controller section 12 allows the micromanipulator 30b to insert a used sample operating needle 35a into a site of the holder 39 where the sample operating needles 35a are not inserted, and to perform a prescribed operation  
15 to remove the used sample operating needle 35a. Thereafter, an operation similar to that performed in the above-mentioned mounting is carried out, whereby the sample operating needles 35a can be exchanged.

Here, the holder 39 may be mounted at any position which the micromanipulator 30b of the sensor unit 10 can access.

20 The above description has been given on the case in which the end effector 35 is a sample operating needle 35a; however, it is needless to say that the end effectors 35 are not limited to sample operating needles 35a, and the end effectors 35 can be automatically mounted and automatically exchanged, for example, by using a holder 39 for other end effectors such as micropipettes. Further, by disposing the  
25 holder 39 for storing a plurality of end effectors 35 at a position which each of the

micromanipulators 30a, 30b can access, a continuous process can be carried out while automatically exchanging the end effectors 35 even if different analyzing processes are to be repeatedly carried out in the analyzing apparatus 1.

Here, the above sample operating needle 35a is not limited to the case in which the micromanipulator 30b picks up a specific sample, but has a structure suitable also for a case in which a person performs a manual operation to pick up a specific sample from within the minute channel.

<5. mechanism for performing an automatic operation of the analyzing apparatus>

As described previously with reference to Fig. 1, the analyzing apparatus 1 is constructed in such a manner that the sample is supplied by using a supplying pot 41 and the sample is taken out and stored by using an extracting pot 51. In such a case where the sample is supplied or extracted by using pots and where the analyzing and extracting operations are carried out continuously and automatically while exchanging plural kinds of samples and reagents, a pot exchanging mechanism is preferably added as an optional device to the analyzing apparatus 1 shown in Fig. 1. In this case, by mounting a plurality of sample pots, reagent pots, and others in the pot exchanging mechanism, analysis work can be automatically performed for plural times while exchanging the samples or reagents. The same applies to the extracting pots, and by mounting a plurality of extracting pots, analysis and extraction work can be automatically carried out by storing a different extract into each extracting pot while exchanging the extracting pots every time a sample to be extracted is guided to the extracting tank 23a.

Fig. 10 is a perspective view illustrating an analyzing apparatus 1 to which a pot exchanging mechanism has been added. Referring to Fig. 10, the analyzing apparatus 1 includes a rotatable supplying disk 40 having a plurality of supplying pots

41 mounted thereon, and a rotatable extracting disk 50 having a plurality of extracting pots 51 mounted thereon in addition to the construction shown in Fig. 1.

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A plurality of sample pots and reagent pots are mounted on the rotatable supplying disk 40, and a rotating motor (not illustrated) is provided as a rotation driving source of the supplying disk on the lower side (rear side) of the central position of the disk. This rotating motor is connected to the controller section 12 in the inside of the sensor unit 10. By controlling the rotating motor with the controller section 12 to control the rotation phase angle of the supplying disk 40, desired sample pot and reagent pot can be moved near to the sample tank 21a and the reagent tank 21b on the analyzing chip 20. When the movement of the desired pots is completed, the micromanipulator 30a is operated to supply the sample and the reagent to each tank on the analyzing chip 20. Further, in order to perform a different reaction on the chip, a plurality of reactions can be carried out automatically by rotating the supplying disk 40 and supplying a sample pot and a reagent pot to the analyzing chip 20 while suitably exchanging the sample pots and the reagent pots.

Similarly, a plurality of extracting pots 51 are mounted on the rotatable extracting disk 50, and a rotating motor (not illustrated) is provided as a rotation driving source of the extracting disk on the lower side (rear side) of the central position of the disk. This rotating motor also is connected to the controller section 12 in the inside of the sensor unit 10. By controlling the rotating motor with the controller section 12 to control the rotation phase angle of the extracting disk 50, a desired extracting pot can be moved near to the extracting tank 23a on the analyzing chip 20. When the movement of the desired pot is completed, the micromanipulator 30b is operated to move the samples such as particles and reaction products as an object of extraction from the extracting tank 23a to the extracting pot 51.

Furthermore, if a different reaction has been carried out on the chip, the extracting disk 50 is rotated to exchange the extracting pots 51 and the sample as an object of extraction is moved to the extracting pot 51.

Thus, by providing a supplying disk 40 and an extracting disk 50 capable of mounting a plurality of pots as a pot exchanging mechanism, an analysis and extraction work can be carried out continuously and automatically for plural times.

On the other hand, there is a case in which the number of use of the analyzing chip 20 comes to a limit or the analyzing chip 20 must be replaced due to change in the contents of analysis. Therefore, an analyzing chip exchanging mechanism is preferably added as an optional device to the analyzing apparatus 1 of Fig. 1. In this case, by mounting a plurality of analyzing chips 20 beforehand in the analyzing chip exchanging mechanism and by automatically exchanging the analyzing chips 20 to be mounted on the sensor unit 10 in accordance with the needs, an analysis work can be carried out continuously and automatically for plural times. Further, a continuous and automatic operation using the analyzing chip exchanging mechanism and the above-mentioned pot exchanging mechanism in combination is also possible.

Fig. 11 is a view illustrating a construction example of an analyzing apparatus 1 in which an analyzing chip exchanging mechanism is disposed. Here, Fig. 11 is a view in which the analyzing apparatus 1 is viewed from a certain point in the direction perpendicular to the YZ-plane of Fig. 1, and illustration of the micromanipulators 30a, 30b is omitted.

In the analyzing apparatus 1 shown in Fig. 1, a stacker 60 and a collector 70 are disposed along the Y-axis direction with the sensor unit 10 sandwiched therebetween.

A pushing-up actuator 17 driven and controlled by the controller section 12 is disposed at a prescribed lower position of the analyzing chip 20 mounted onto the sensor unit 10. In exchanging the analyzing chips 20 on the sensor unit 10, the controller section 12 in the sensor unit 10 operates the pushing-up actuator 17, and  
 5 lifts the analyzing chip 20 from the hollowed portion in the upper part of the sensor unit 10 (the carved part for inserting the analyzing chip 20). At this time, the position of the lower surface of the analyzing chip 20 is set to be higher than the height of the bank of the hollowed portion of the sensor unit 10. As the push-up actuator 17, a plunger-type magnet, for example, can be utilized.

10 A storing section 61 for storing unused analyzing chips 20, a chip elevator 62 disposed at a lower part of the storing section 61, and a chip pushing-out mechanism 63 for pushing the analyzing chip 20 out to the hollowed portion of the sensor unit 10 are provided in the stacker 60. In exchanging the analyzing chips 20, the chip elevator 62 is operated to lift the analyzing chips 20 up so that the position of  
 15 the lower surface of the uppermost analyzing chip 20 among the plurality of analyzing chips 20 stored in the storing section 61 will be a little higher than the bank of the hollowed portion of the sensor unit 10. Thereafter, the chip pushing-out mechanism 63 is operated to push the analyzing chip 20 out to a position above the hollowed portion of the sensor unit 10. When the amount of pushing-out the analyzing chip  
 20 20 by the chip pushing-out mechanism 63 exceeds a prescribed amount, the push-up actuator 17 of the sensor unit 10 stops, and the pushing-up member returns to the state before the start of the operation. When the analyzing chip 20 reaches the hollowed portion of the sensor unit 10, the analyzing chip 20 falls into the hollowed portion by its self-weight, whereby the analyzing chips 20 are exchanged. The  
 25 analyzing chip 20 mounted to the sensor unit 10 is pushed out by the tip end of the



unused analyzing chip 20, which has been pushed out from the stacker 60, to move from above the sensor unit 10 towards a place where the collector 70 is disposed, and is let fall into the collector 70 by its self-weight.

By adopting the above-mentioned construction, the analyzing chips 20  
5 mounted on the sensor unit 10 can be automatically exchanged in accordance with the needs, whereby the analysis work can be carried out continuously and automatically for plural times.

Here, as the above-mentioned chip elevator 62, a mechanism of lifting the  
elevator floor 62c up and down by combining a micromotor 62a and a thread  
10 mechanism 62b can be utilized, for example. Further, the chip pushing-out mechanism 63 can be constructed by combining a micromotor 63a with a rack 63b and using the rack 63a as the pushing-out member. Here, the chip elevator 62 and the chip pushing-out mechanism 63 are connected to the controller section 12 as shown in Fig. 11, and receive an operation control from the controller section 12. On the  
15 other hand, the stacker 60 itself may have an independent controller section, and the operations of the chip elevator 62 and the chip pushing-out mechanism 63 may be controlled by the controller section on the stacker 60 side.

Furthermore, by providing a holder 39 that stores a plurality of end effectors side by side for exchanging the end effectors 35 of the above-mentioned  
20 micromanipulators 30a, 30b, the end effectors 35 can be automatically exchanged in accordance with the needs, so that the analysis work can be carried out continuously and automatically.

Thus, by combining micromanipulators 30a, 30b or an exchanging mechanism for supplying various source materials with the analyzing apparatus 1, the  
25 analysis work can be carried out automatically and the required samples can be

extracted automatically.

<6. modified examples>

As shown above, one embodiment of the present invention has been described; however, the present invention is not limited to the contents of the above  
5 descriptions alone.

For example, in the above description, a case has been exemplified in which the analysis and manipulations are carried out by hybridization reaction of DNA. However, it is needless to say that this analyzing apparatus can be applied to a case in which analysis and manipulations are carried out utilizing an antibody-antigen  
10 reaction, a ligand-receptor reaction, or other biotic or biochemical reactions. In other words, it is sufficient that the samples as an object of analysis and manipulations in the analyzing apparatus is a minute substance.

Further, in the above descriptions, a case has been exemplified in which electrophoresis is utilized as a method for moving solutions or samples such as  
15 samples and reagents among the tanks on the analyzing chip 20; however, a different method may be adopted. For example, pressure generated by a micropump may be utilized or a gravity potential may be utilized by varying the height positions of the tanks.

While the invention has been shown and described in detail, the foregoing  
20 description is in all aspects illustrative and not restrictive. It is therefore understood that numerous other modifications and variations can be devised without departing from the scope of the invention.

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What is claimed is:

1. A microchip comprising:

5 a channel having at least one internal surface, wherein an object to be analyzed is capable of traveling through said channel; and

an optical element facing said channel to receive a light from said object, said optical element having a surface forming a part of said at least one internal surface of said channel.

10 2. A microchip as claimed in claim 1,

wherein at least a portion of said at least one internal surface of said channel is defined by a groove formed on a first surface of a substrate;

wherein said substrate has a second surface oppose to said first surface and has a through hole connecting a bottom of said groove and said second surface, and

15 wherein said optical element is provided in said through hole.

3. A microchip as claimed in claim 2, wherein said through hole has a tapered shape.

20 4. A microchip as claimed in claim 2, further comprising:

a cover plate provided on said first surface of said substrate, said cover plate covering at least a portion of said groove.

5. A microchip as claimed in claim 1, wherein said optical element comprises a  
25 condenser lens.

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6. A microchip as claimed in claim 1, further comprising:

a first electrode provided on said at least one internal surface of said channel; and

5 a second electrode provided on said at least one internal surface of said channel at a vicinity of said optical element.

7. A microchip as claimed in claim 6,

10 wherein said object is capable of traveling through said channel in a traveling direction, and

wherein said second electrode is provided at an upstream side of said optical element with respect to said traveling direction.

8. A microchip as claimed in claim 1, further comprising:

15 a light guide for guiding a light from an external light source to a prescribed area of said channel,

wherein said optical element is provided at said prescribed area.

9. A microchip comprising:

20 a channel extending in an extending direction, wherein an object to be analyzed is capable of traveling through said channel; and

deflecting electrodes for deflecting said object in a direction traverse to said extending direction at a vicinity of an analyzing position by being applied with electrical signals thereto.

10. A microchip as claimed in claim 9, further comprising:

terminals electrically connected with said deflecting electrodes,  
respectively,

wherein said terminals are for electrically connecting said deflecting  
5 electrodes with an external controller that generates said electrical signals.

11. A microchip as claimed in claim 9,

wherein said object is capable of traveling through said channel in a  
traveling direction, and

10 wherein one of said deflecting electrodes is provided at an upstream side of  
said analyzing position with respect to said traveling direction.

12. A microchip as claimed in claim 9, further comprising:

an optical element facing said channel at said analyzing position, said  
15 optical element being for receiving a light from said object.

13. A manipulating needle for manipulating an object, said needle comprising:

an edge portion having a diameter not larger than 50  $\mu\text{m}$ , wherein a material  
having a capability of a biochemical bond with said object or a capability of a biotic  
20 bond with said object is adhered to said edge portion.

14. A manipulating needle as claimed in claim 13, wherein said diameter is in a  
range from 1  $\mu\text{m}$  to 50  $\mu\text{m}$ .

25 15. A manipulator for manipulating an object under a control from an external

manipulating apparatus, said manipulator comprising:

an edge portion to which a material having a capability of a biochemical bond with said object or a capability of a biotic bond with said object is adhered; and

an attachment portion for being detachably attached with said external  
5 manipulating apparatus.

16. A manipulator as claimed in claim 15, wherein said attachment portion is made of a magnetic material.

10 17. An analyzing apparatus comprising:

a holder for detachably holding an analyzing microchip, said analyzing microchip comprising a channel having at least one internal surface, wherein an object to be analyzed is capable of traveling through said channel; and

a sensor unit, provided in said holder, for receiving a light from an analyzing  
15 position of said channel thereby a light from said object is detected by said sensor when said object travels said analyzing position.

18. An analyzing apparatus as claimed in claim 17, further comprising a light source for projecting a light to said analyzing position.

20

19. An analyzing apparatus as claimed in claim 17, wherein said sensor unit comprising:

a condenser lens for condensing said light from said analyzing position; and

a photo-diode for sensing said condensed light.

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20. An analyzing apparatus as claimed in claim 17, wherein said holder having a hollowed portion in which said microchip is to be located.

21. An analyzing apparatus comprising:

- 5           a holder for detachably holding a microchip, said microchip comprising:  
            a channel extending in an extending direction, wherein an object  
to be analyzed is capable of traveling through said channel; and  
            deflecting electrodes at least one of which is provided at a vicinity  
of an analyzing position; and  
10           a controller, provided in said holder, for applying electrical signals to said  
deflecting electrodes,  
            wherein said deflecting electrodes deflects said object in a direction traverse  
to said extending direction at said analyzing position when said controller applies  
said electrical signals to said deflection electrodes.

15

22. An analyzing apparatus as claimed in claim 21, wherein said holder having a hollowed portion in which said microchip is to be located.

23. An analyzing apparatus as claimed in claim 21, further comprising terminals,  
20   provided on said holder, for electrically connecting said controller and said deflecting  
electrodes.

24. An analyzing apparatus comprising:

- a holder for detachably holding an analyzing microchip, said analyzing  
25   microchip comprising a channel having at least one internal surface, wherein an

a lifting unit, provided in said holder, for lifting said analyzing microchip.

25. An analyzing apparatus as claimed in claim 24,

5 wherein said holder having a hollowed portion in which said microchip is to  
be located, and

wherein said lifting unit is provided under said hollowing portion.

26. An analyzing apparatus as claimed in claim 24, further comprising:

10                    a controller, electrically connected with said lifting unit, for controlling said  
lifting unit.

27. A method of picking up an object traveling in a traveling direction through a channel formed in an analyzing microchip, said method comprising:

15 sensing said object at an analyzing position of said channel;

moving, in response to said sensing of said object, a manipulator into a pick up position of said channel that is downstream side of said analyzing position with respect to said traveling direction, wherein at least a part of said manipulator is made of a material having a characteristic of a biochemical bond capability with said object or a biotic bond capability with said object; and

retrieving said object by said manipulator by using said characteristic of said material.

28. A method as claimed in claim 27, further comprising:

25 scanning said manipulator at said pick up position while said retrieving step



is executed.

29. A method as claimed in claim 28, wherein said manipulator is scanned in a direction traverse to said traveling direction.

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## ABSTRACT OF THE DISCLOSURE

One of the principal objects of the present invention is to realize, in a small scale and at a low cost, an analyzing apparatus that analyzes and manipulates a minute sample such as DNA. The analyzing apparatus 1 incorporates an optical  
5 system for measuring a fluorescence from a sample traveling through a minute channel 24c. Specifically, a light source that generates a light for exciting a fluorescence of the sample and a light guide that guides the light from the light source to the minute channel 24c are provided, whereby the fluorescence of the sample in the minute channel 24c is well excited. In order to observe the fluorescence of the  
10 sample, a condensing optical element 26, provided on a wall surface of the minute channel 24c, for capturing the fluorescence from the sample, and a sensor section 11 are provided, whereby the fluorescence of the sample in the minute channel 24c can be well observed.

FIG. 1

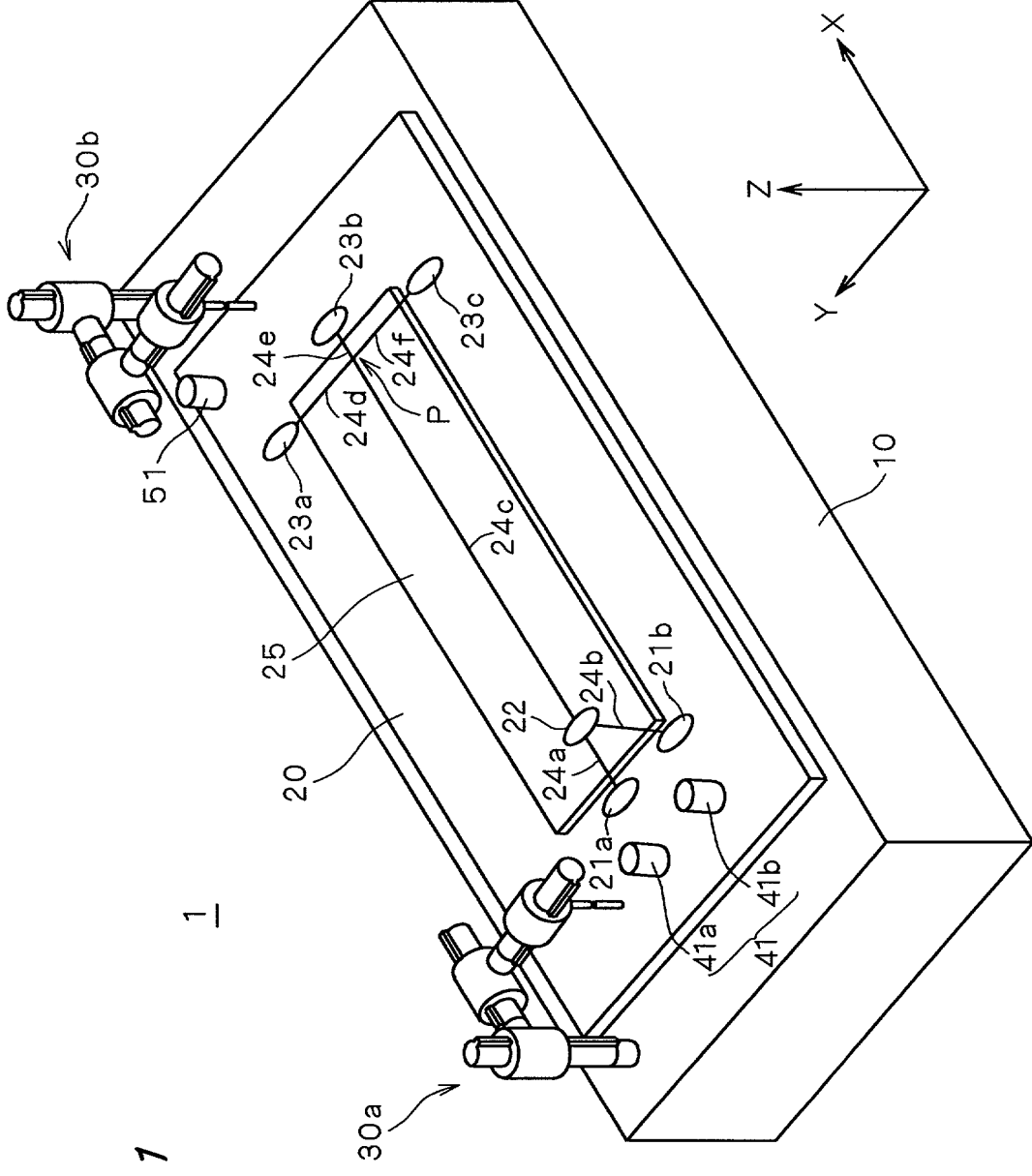


FIG. 2

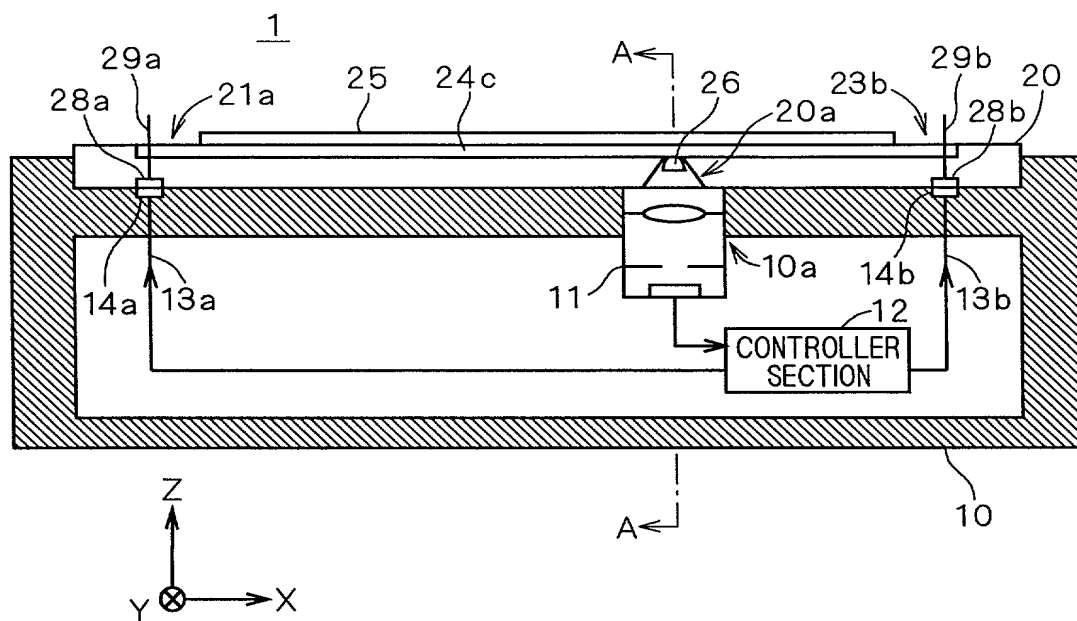


FIG. 3

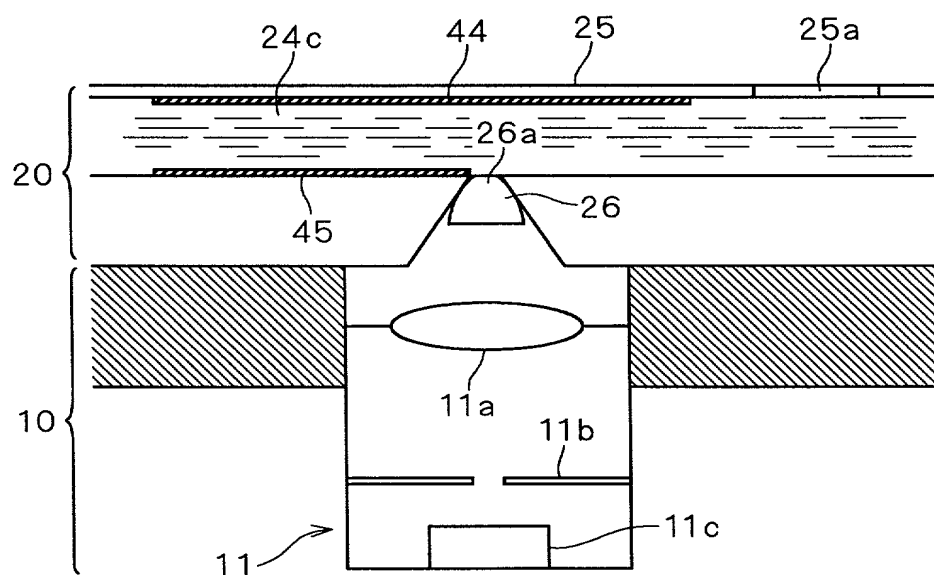
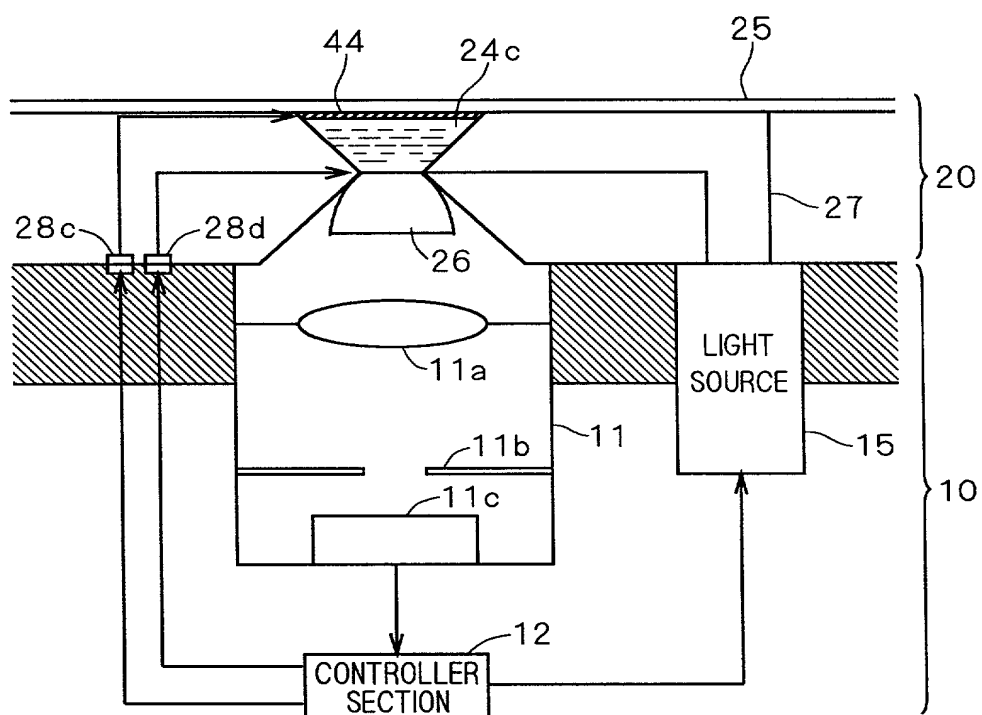


FIG. 4



A - A

FIG. 5

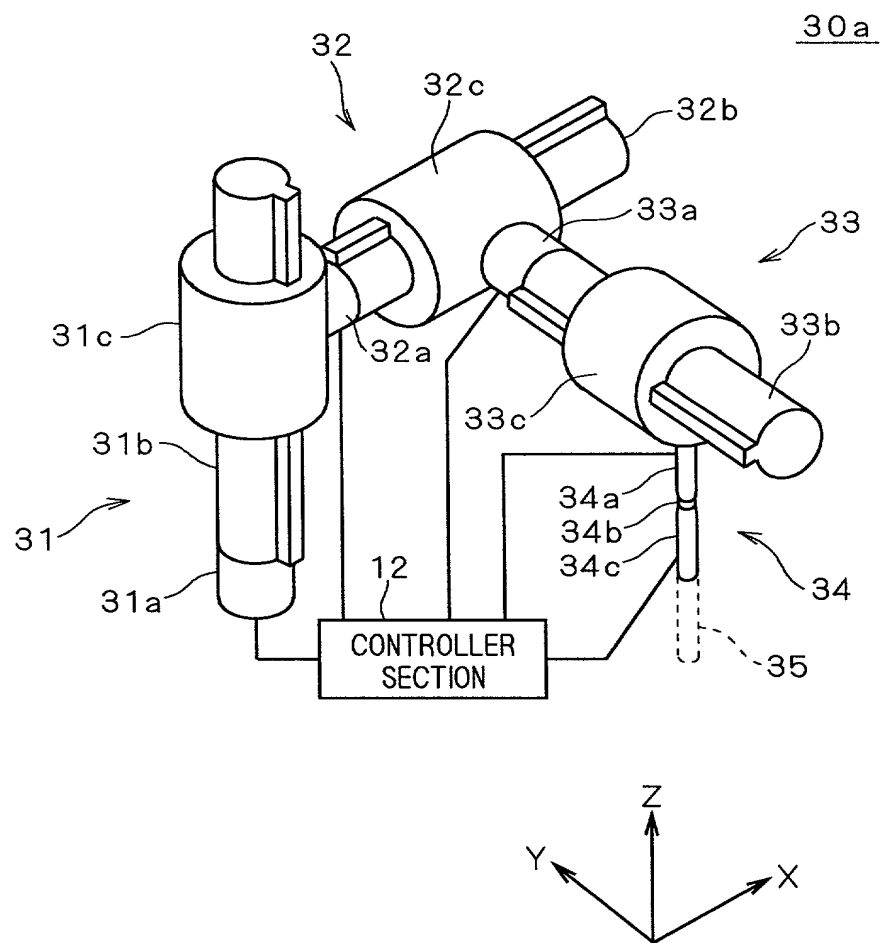


FIG. 6A

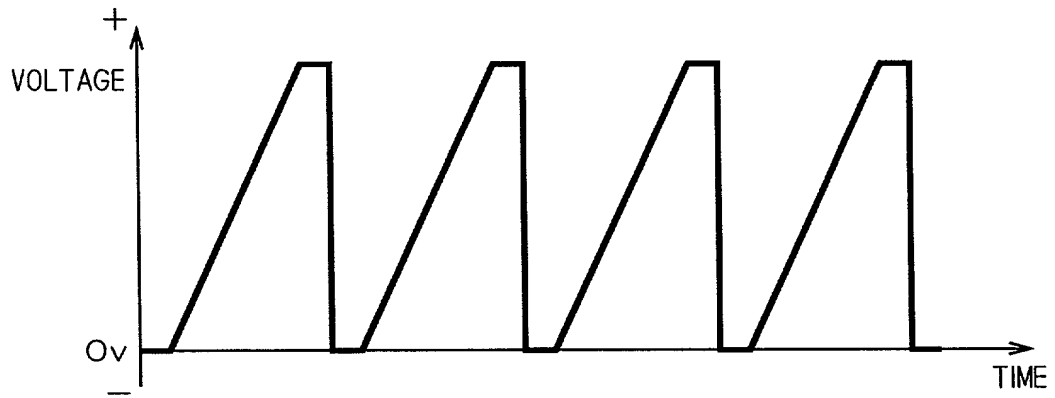


FIG. 6B

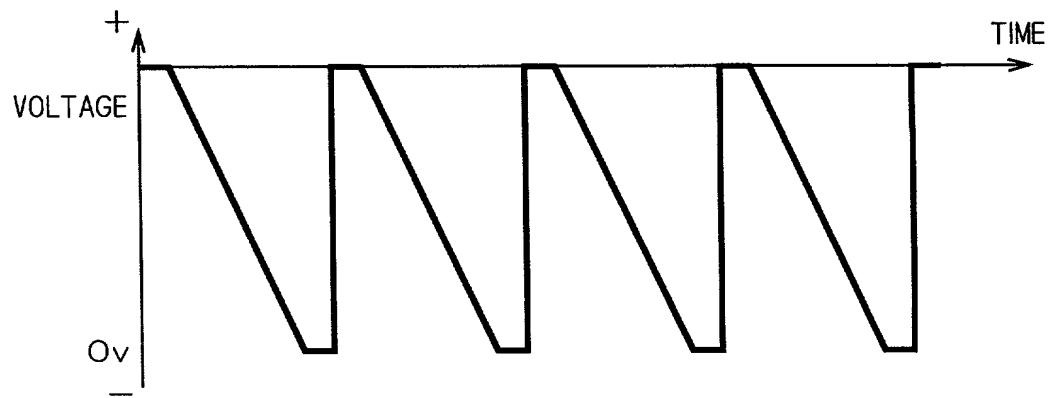


FIG. 7

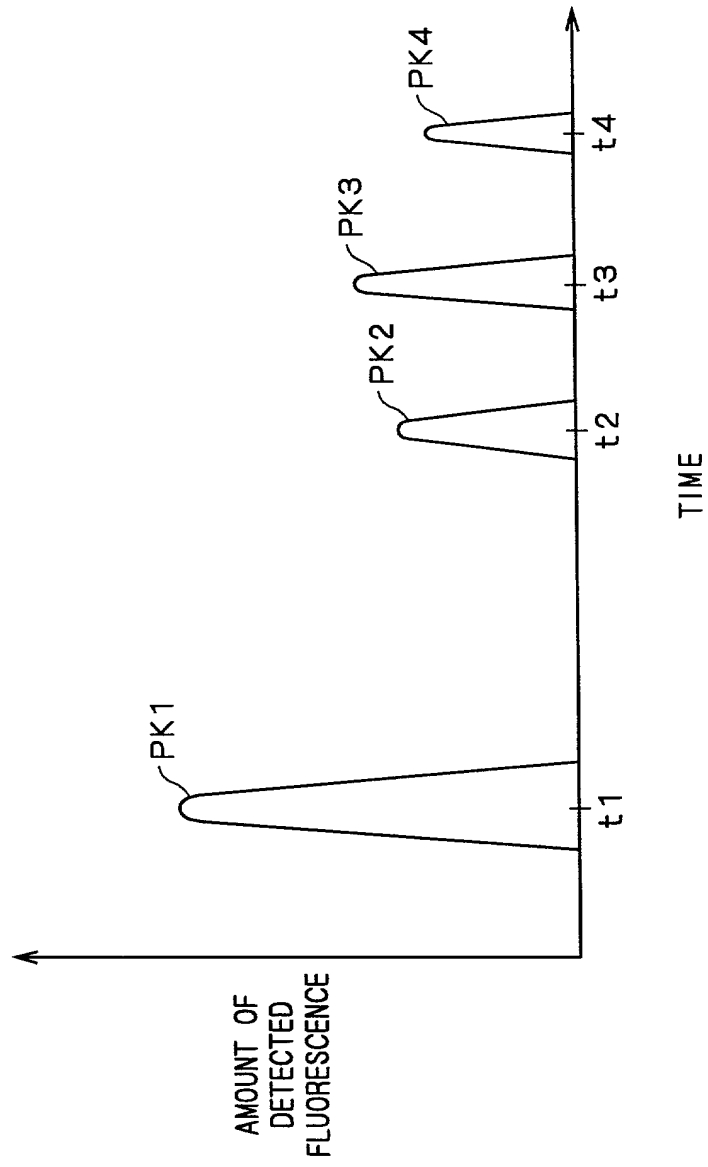




FIG. 8

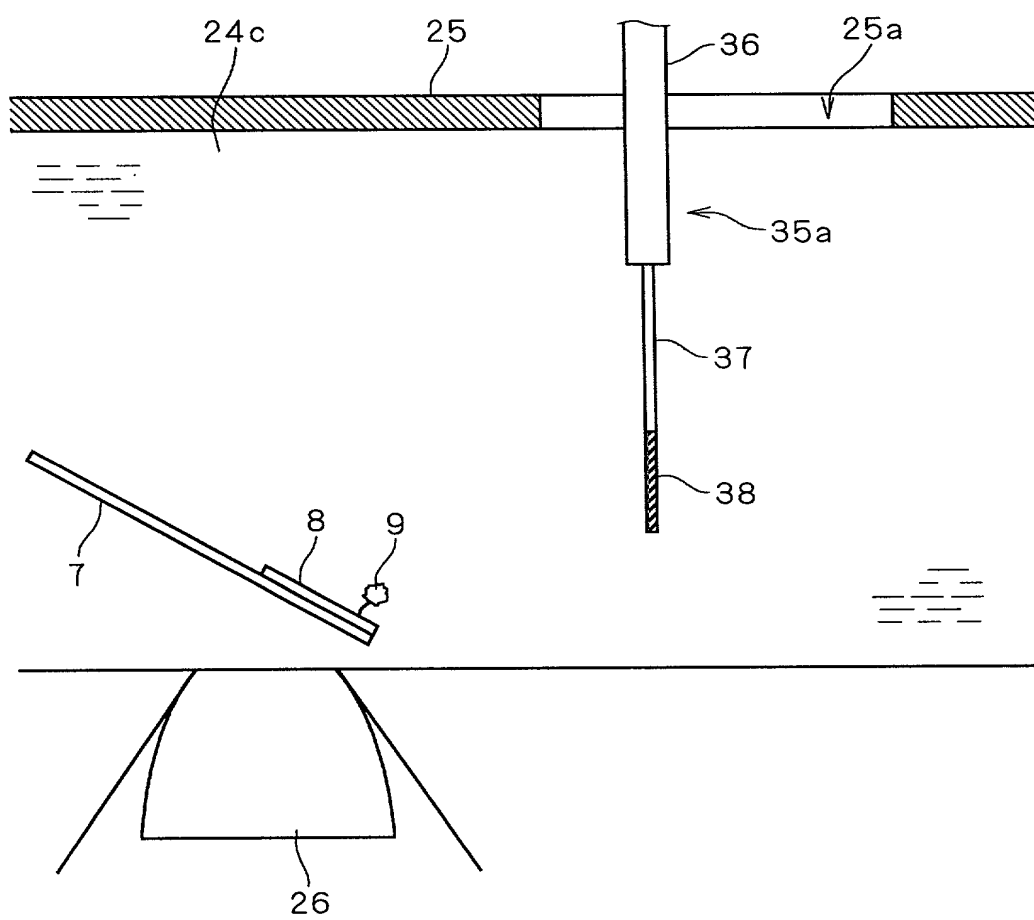
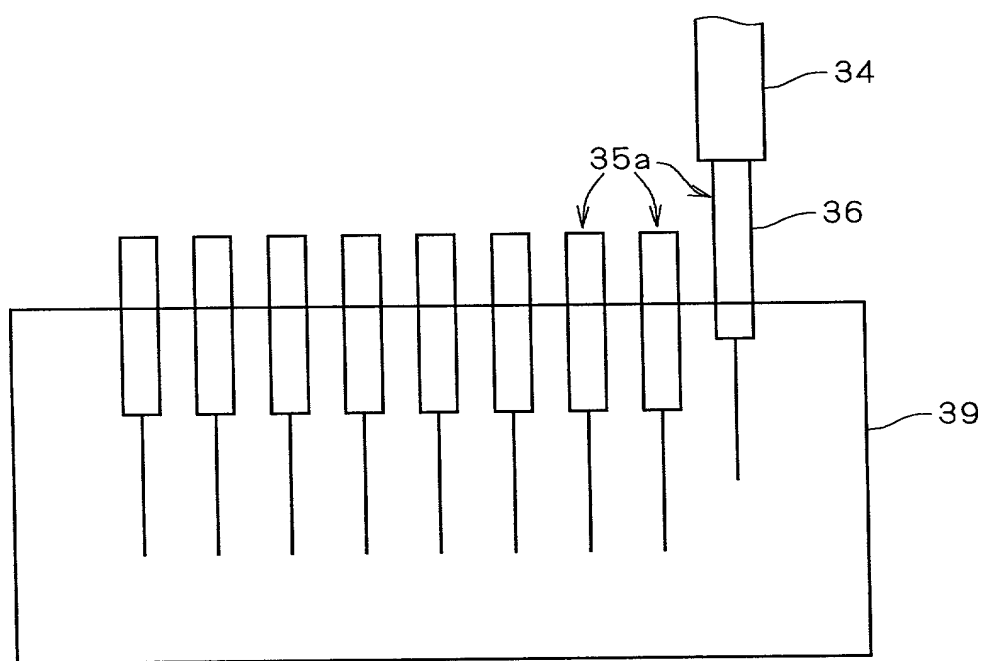


FIG. 9



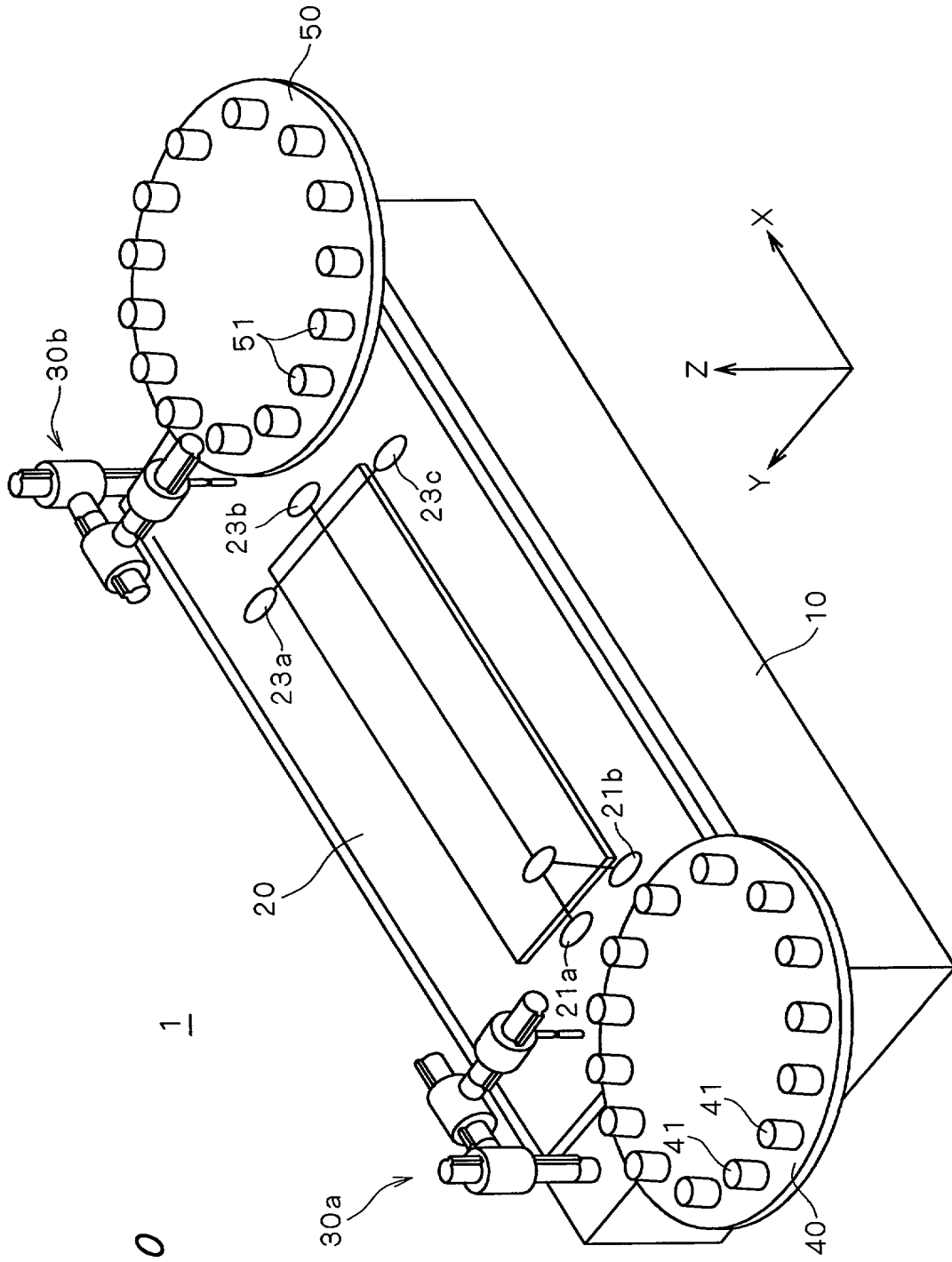
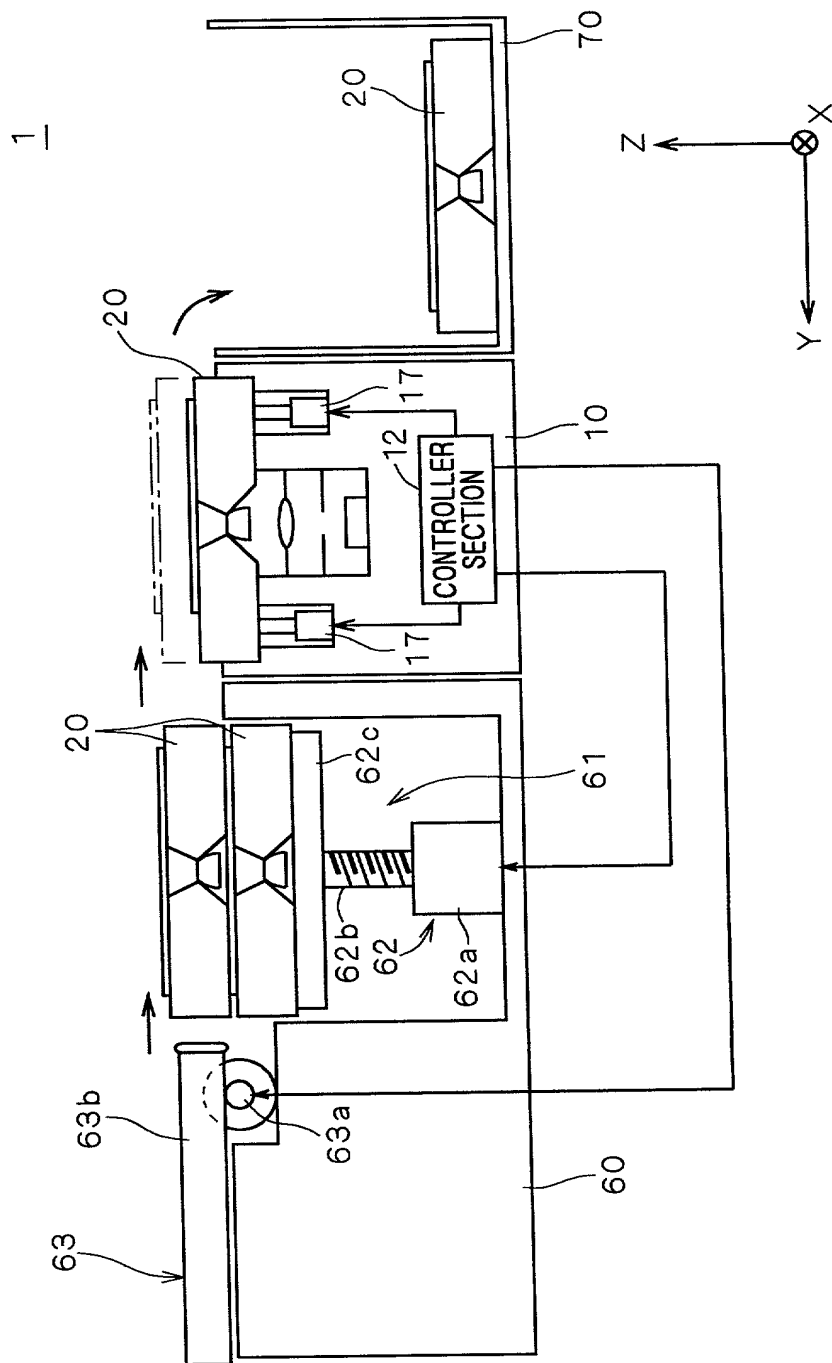


FIG. 11



代理人の案件番号:

Attorney Docket No.:

特許出願宣誓書および委任状

DECLARATION AND POWER OF  
ATTORNEY FOR PATENT APPLICATION

私は、以下に記載された発明者として、こ  
こに下記の通り宣言する:

As a below named inventor, I hereby declare  
that:

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の後に記載された通りである。

My residence, post office address, and  
citizenship are as stated next to my name.

下記の名称の発明について、特許請求の範  
囲に記載され、かつ特許が求められている発  
明主題に関して、私は、私が最初、最先かつ  
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ている場合)か、または、私と以下に記載さ  
れた他の者が最初、最先かつ共同発明者であ  
る(複数の氏名が記載されている場合)と、  
信じている。

I believe that I am the original, first, and sole  
inventor (if only one name is listed below) or I  
and the other person(s) listed below are the  
original, first, and joint inventors (if plural names  
are listed below) of the subject matter which is  
claimed and for which a patent is sought on the  
invention entitled

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unless the following box is checked:

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☐ was filed on

以下の米国出願番号を有し、

as United States Application Number

または、以下のPCT国際出願番号を有し、

or PCT International Application Number

かつ、以下の日に補正されている

and was amended on

(該当する場合)。

(if applicable).

私は、上記の補正書によって補正された、特許請求の範囲を含む上記明細書を検討し、かつ内容を理解していることをここに表明する。

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

私は、連邦規則法典第37編規則1.56に定義されている、特許性について重要な情報を開示する義務があることを認める。

I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, Section 1.56.

私は、ここに、以下に記載した外国での特許出願または発明者証の出願、或いは米国以外の少なくとも一国を指定している米国法典第35編第365条(a)項によるPCT国際出願について、同第119条(a)-(d)項または第365条(b)項に基づいて優先権を主張するとともに、優先権を主張する本出願の出願日より前の出願日を有する外国での特許出願または発明者証の出願、或いはPCT国際出願については、いかなる出願も、下記のボックスをチェックすることにより示した。

I hereby claim foreign priority under Title 35, United States Code, Section 119(a)-(d) or 365(b) of any foreign application(s) for patent or inventor's certificate, or 365(a) of any PCT international application which designated at least one country other than the United States listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or PCT international application having a filing date before that of the application on which priority is claimed.

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PRIOR FOREIGN APPLICATION(S)  
(外国での先行出願)

Priority  
Not Claimed  
(優先権主張なし)

P11-289319	Japan	12/10/1999	<input type="checkbox"/>
(Number) (番号)	(Country) (国名)	(Day/Month/Year Filed) (出願日/月/年)	
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(Number) (番号)	(Country) (国名)	(Day/Month/Year Filed) (出願日/月/年)	
<hr/>			<input type="checkbox"/>

私は、ここに、下記のいかなる米国仮特許出願についても、その米国法典第35編119条(e)項の利益を主張する。

I hereby claim the benefit under Title 35, United States Code, Section 119(e) of any United States provisional application(s) listed below.

<hr/>	<hr/>
(Application Number) (出願番号)	(Filing Date) (出願日)
<hr/>	<hr/>
(Application Number) (出願番号)	(Filing Date) (出願日)

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I hereby claim the benefit under Title 35, United States Code, Section 120 of any United States application(s), or 365(c) of any PCT international application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT international application in the manner provided by the first paragraph of Title 35, United States Code, Section 112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, Section 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of application.

(Application Number)  
(出願番号)

(Filing Date)  
(出願日)

(Status: Patented, Pending, Abandoned)  
(現状：特許許可、係属中、放棄)

(Application Number)  
(出願番号)

(Filing Date)  
(出願日)

(Status: Patented, Pending, Abandoned)  
(現状：特許許可、係属中、放棄)

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.



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Customer Number: 24367



24367

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Direct telephone calls to:

James W. Williams

James W. Williams

ダイレクトイン: (214) 981-3328

Direct No.: (214) 981-3328

代表電話番号: (214) 981-3300

Main No.: (214) 981-3300

代理人の案件番号:

Attorney Docket No.:

Full name of sole or first joint inventor:

唯一または第1発明者の氏名:

Yoshiaki

HATA

First  
(名)

Middle  
(ミドルネーム)

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